Conferences and Reviews

Hormonal Therapy for Stage D Cancer of the Prostate

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Adenocarcinoma of the prostate is the most common malignant neoplasm occurring in men. About half of patients present with metastatic disease. The mainstay of the treatment of stage D cancer of the prostate is hormonal therapy. Bilateral simple orchiectomy remains the gold standard with which other therapies must be compared. Luteinizing hormone-releasing hormone analogues and antiandrogens are now most commonly used but are costly. Initiating hormonal therapy immediately on diagnosing metastatic disease appears to have some advantage over delaying therapy until a patient is symptomatic. Total androgen blockade also appears to be beneficial in terms of survival but at high cost.

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Adenocarcinoma of the prostate, the most common malignant tumor occurring in men, was newly diagnosed in 165,000 men in 1993.[1]* As the second leading cause of death from cancer in men, it accounts for 35,000 deaths per year.[1] Half of patients may have metastatic or stage D disease (Table 1)[2,3] at diagnosis. Fortunately, more than 80% of these patients will respond symptomatically to hormonal therapy.[4] The androgen sensitivity of prostate cancer and the tumor regression that follows bilateral orchiectomy was first recognized by Huggins and Hodges in 1941, establishing "androgen deprivation" as the mainstay of therapy for advanced prostate cancer (Table 2).[5]

Despite hormonal therapy, androgen insensitivity eventually develops in nearly all patients with advanced prostate cancers. More than 85% of patients with stage D1 disease will have progression of their disease within five years.[6,7] Patients with stage D2 disease have a median survival of only 30 months and a five-year survival of 20%.[6,7] Progression to stage D3 disease with the development of androgen insensitivity usually occurs 12 to 16 months after endocrine therapy is initiated.[6,7] Following progression after hormonal therapy, half of patients die within six months of relapse.[8,9] The mean survival of patients presenting with metastatic disease is 1.8 years.[9]

The criteria for initiating hormonal therapy for prostate cancer have included the presence of metastatic disease, localized disease in older men not candidates for surgical or radiation therapy, and recurrence after surgical or radiation therapy. Numerous prognostic factors have been identified that favorably affect progression-free survival after the initiation of hormonal therapy. These have included performance status according to criteria established by the Eastern Cooperative Oncology Group (ECOG)[10-12]; the extent of disease by bone scan[13,14]; an acid phosphatase level less than two times normal[13]; an alkaline phosphatase level of less than 115 U per liter[11,15]; pain before the initiation of therapy[11]; a serum testosterone level of greater than 250 nmol per liter[11,16]; and tumor size.[13] Three studies that used multivariate analyses found ECOG performance status to be the most predictive of response and median time to failure.[11,12,15]

Androgen Production

The production of androgens in humans is mediated through the hypothalamic-pituitary-testicular axis (Figure 1). The hypothalamus detects decreased serum testosterone and secretes luteinizing hormone-releasing hormone (LH-RH) that migrates to the anterior pituitary through the hypophyseal portal system of veins. Under the stimulation of LH-RH, the anterior pituitary gland secretes luteinizing hormone. Luteinizing hormone release stimulates androgen production by Leydig cells located in the interstitium of the testes. The testes secrete primarily testosterone, but other steroids are secreted in smaller quantities such as dihydrotestosterone, androsterone, androstenedione, progesterone, and 17-hydroxyprogesterone. Testosterone circulates largely bound to serum proteins including albumin (54%) and testosterone-binding globulin (44%). Only the unbound fraction is active. Testosterone is converted in the prostate to dihydrotestosterone, a more potent androgen, by the enzyme 5α-reductase. Only a small portion of dihydrotestosterone is produced directly by the testes. High circulating levels of testosterone, as well as estrogen, inhibit the release of both luteinizing hormone by the pituitary and LH-RH by the hypothalamus.

The adrenal gland is a source of weak androgens such

*See also the editorial by F. V. Mayer, MD, "Future Trends in the Incidence and Management of Prostate Cancer," on pages 380-381 of this issue.

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ABBREVIATIONS USED IN TEXT

DES = diethylstilbestrol
ECOG = Eastern Cooperative Oncology Group
FSH = follicle-stimulating hormone
LH-RH = luteinizing hormone-releasing hormone
PSA = prostate-specific antigen
VACURG = Veterans Administration Cooperative Urological Research Group

as androstenedione and dehydroepiandrosterone, which together account for 10% or more of circulating androgens and are not under the direct control of luteinizing hormone.

Surgical Castration

Since the benefits of androgen ablation were established in patients with advanced prostate cancer,[5] bilateral orchiectomy, which provides prompt castrate levels of testosterone (< 50 nmol per liter), remains the standard with which all other forms of therapy are compared.[17-19] The procedure has low morbidity and mortality.[17,20,21] Possible advantages of orchiectomy include lower cost (Table 3), rapid response, and therapeutic compliance. Serious side effects from orchiectomy include a loss of libido, impotence (100%), and mild to severe hot flashes.[22] Subcapsular orchiectomy may be more psychologically appealing to some patients. The procedure has been criticized because of the possibility of incomplete removal of functioning tissue; however, studies have shown that testosterone is reduced to castrate levels and remains so even after stimulation with human chorionic gonadotropin.[23,24]

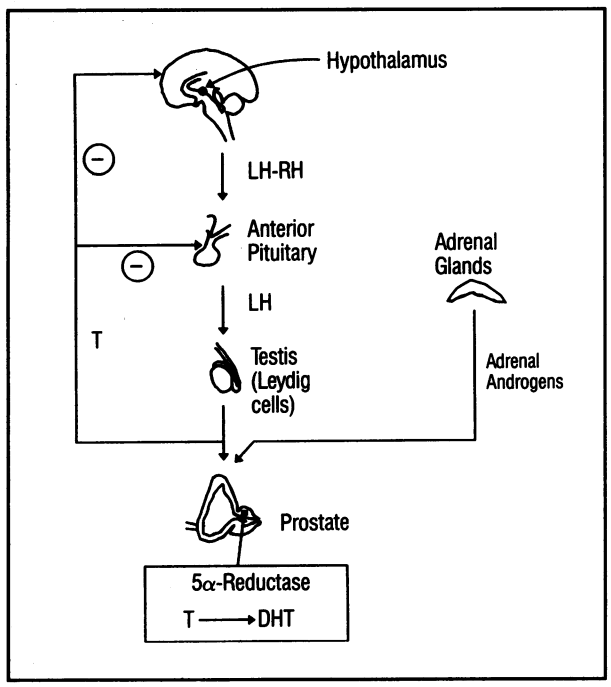

Figure 1.—The diagram shows the mechanism of the production of androgens through the hypophyseal-pituitary-gonadal axis. The hypothalamus secretes luteinizing hormone-releasing hormone (LH-RH) in a pulsatile manner, regulating the release of luteinizing hormone (LH) by the anterior pituitary gland. Luteinizing hormone then stimulates the secretion of testosterone (T) by Leydig cells in the testes. Testosterone is reversibly bound to albumin and testosterone-binding globulin so that only about 2% remains in the unbound active fraction. Testosterone in turn regulates LH-RH and LH by negative feedback (−). The adrenal glands also contribute androgens such as androstenedione and dehydroepiandrosterone under the control of corticotropin that is released from the anterior pituitary by stimulation from corticotropin-releasing factor and vasopressin from the posterior pituitary. Testosterone is converted to the more potent dihydrotestosterone (DHT) within the prostate by the enzyme 5α-reductase.

TABLE 1.—*Staging System for Patients With Stage D (Advanced) Prostate Cancer**

Prostatic Cancer Stage	*Clinical Criteria*
D0	Localized disease with a normal bone scan but serum acid phosphatase level elevated × 2
D1	Pelvic lymph node involvement
D2	Evidence of distant metastases in bone or other organs
D3	Relapse in the presence of D2 disease after adequate endocrine therapy

*From Whitmore,[2] modified by Jewett.[3]

Medical Castration

Estrogens

In the treatment of prostate cancer, estrogens function primarily by ablating the release of luteinizing hormone by the anterior pituitary gland and thereby removing the stimulation of testosterone production by the testes. Estrogens also increase the synthesis of testosterone-binding globulin by the liver, inhibit the functions of 5α-reductase, and inhibit dihydrotestosterone binding both to its receptor and to DNA polymerase. Evidence of a direct cytotoxic effect of estrogens on prostate cancer cells has been shown.[25-27]

Diethylstilbestrol (DES) has historically been the most commonly used estrogen in the treatment of prostate cancer. A dose of DES, 3 mg orally daily, provides castrate levels of testosterone in 7 to 21 days.[22,28] Even 1 mg per day may achieve castrate levels of serum testosterone in most but not all patients.[29] In the first Veterans Administration Cooperative Urological Research Group study (VACURG I), patients taking 5 mg of DES had increased cardiovascular complications compared with controls. The second study, VACURG II, showed that administering this hormone in a dosage of 1 mg per day was as effective as giving 5 mg per day with fewer cardiovascular side effects, although castrate levels of testosterone were not consistently obtained.[31,32] Complications of DES therapy include salt and water retention, gynecomastia and breast tenderness, nausea and vomiting, thromboembolic events—reported to be 300% higher than in age-matched populations[33]—loss of libido, impotence, and an increased incidence of cardiovascular disease. Although DES is inexpensive (see Table 3) and its use obviates the need for an operation, it is now used less frequently due to improved toxicity profiles of newer drugs. Estramustine, an estrogenic agent combined with a nitrogen mustard moi-

TABLE 2.—*Endocrine Therapies for Prostate Cancer*

Therapy	*Type*
Surgical castration	Bilateral simple orchiectomy, bilateral subcapsular orchiectomy
Medical castration	Estrogens: diethylstilbestrol; LH-RH agonists or antagonists: leuprolide acetate, goserelin, buserelin
Antiandrogens	Androgen receptor antagonists: flutamide, nilutamide, casodex; 5α-reductase inhibitors: finasteride; steroidal antiandrogens: megestrol acetate, cyproterone acetate
Adrenal suppression	Surgical adrenalectomy; medical adrenalectomy: ketoconazole, aminoglutethimide
Direct cytotoxic effect	Stilbestrol diphosphate

LH-RH = luteinizing hormone-releasing hormone

ety to provide specific cell toxicity, was shown to have no advantage over DES for primary therapy.[34]

Luteinizing Hormone-Releasing Hormone Agonists or Antagonists

The LH-RH analogues have an amino acid substitution glycine 6 with leucine and deletion of a terminal amino amide group that gives them a higher affinity for LH-RH receptors in the anterior pituitary than does native LH-RH.[35] Administering a bolus of an LH-RH analogue causes a release of luteinizing hormone and an increase in testosterone production called the "flare" phenomenon.[36] Long-term administration of LH-RH analogues disrupts the pulsatile release of gonadotropin-releasing hormone with an inhibition of LH-RH receptors that paradoxically causes gonadotropin suppression.[35] Serum testosterone levels reach castrate levels within four weeks of starting treatment in 90% of men.[37] Luteinizing hormone-releasing hormone analogues maintain plasma testosterone levels in the castrate range for the duration of therapy.[38]

Several studies have examined the efficacy of LH-RH analogues versus DES or orchiectomy. The Leuprolide Study Group randomly assigned 199 previously untreated patients with metastatic prostate cancer to receive either subcutaneous leuprolide acetate, 1 mg per day, or DES, 3 mg per day.[39] Time to progression was similar in the two groups, with no significant difference in one-year survival (87% for leuprolide versus 78% for DES treatment). Fewer cardiovascular complications and less gynecomastia occurred in the leuprolide-treated cohort. A randomized trial comparing the use of the LH-RH analogue buserelin with that of DES or orchiectomy in 160 patients with stage D2 disease showed no notable differences between treatment groups for progression-free survival, best response, or overall survival.[40] The treatment efficiency of the LH-RH analogue is equivalent to that of either DES or orchiectomy.[37,40] No one analogue has proved superior to another.[41] Major side effects of treatment with LH-RH analogues include hot flashes (an incidence as high as 72%),[13,37] gynecomastia (12% to 16%),[13,37,38] irritation at the injection site (12%),[37] and the flare phenomenon.

The initial stimulation of testosterone production by the increased release of luteinizing hormone may be associated with increased bone pain four to ten days after starting a regimen of an LH-RH analogue. This flare phenomenon usually resolves spontaneously. In patients who have spinal metastases and particularly those with lower extremity motor deficits, the use of LH-RH analogues is contraindicated because spinal cord compression may occur during the flare, leading to paralysis. Impending ureteral obstruction is also a contraindication to the use of LH-RH analogues alone. Antiandrogens such as flutamide or DES have been used effectively to block the flare phenomenon in the first two weeks of LH-RH analogue therapy.[42,43]

The two LH-RH analogues that are approved by the United States Food and Drug Administration include leuprolide acetate and goserelin. Both are available in depot preparations that require once-a-month injections: Lupron Depot (TAP Pharmaceuticals) and Zoladex (ICI Americas), respectively. Depot preparations have been shown to be as effective as once-a-day administration.[36] Lupron Depot is administered intramuscularly, and Zoladex is deposited as a pellet through a 14-gauge needle subcutaneously. Monthly administration improves patient acceptance and compliance but is expensive (see Table 3).

Antiandrogens

Flutamide. Flutamide is a nonsteroidal anilide and a potent antiandrogen. Administered as an oral dose of 250 mg three times a day, flutamide appears to inhibit the uptake and binding of testosterone and dihydrotestosterone to nuclear receptors, producing a secondary increase in serum testosterone levels.[44-46] Because serum testosterone levels are maintained, a major advantage of flutamide and other nonsteroidal antiandrogens used as monotherapy is the preservation of potency. Flutamide has been more commonly used in combination therapy to achieve total androgen blockade (see Total Androgen Blockade).

In one study, 73 previously untreated patients with stage D prostate cancer were given flutamide monotherapy.[47] Most patients (85%) had a favorable response lasting 2 to 56 months (mean 12.5 months) as determined by a decreased prostatic acid phosphatase level, a decreased number of bony metastases, decreased bladder outlet obstruction, and a decrease in prostate size and pain. Sexual potency was preserved in 86% of patients. Several randomized prospective trials show that using flutamide alone is as effective as DES in the treatment of advanced prostate cancer.[48-50] In one small randomized trial, the use of flutamide, 750 mg per day, was compared with that of DES, 3 mg per day.[49] An objective response or stabilization of disease was seen in 13 of 20 patients receiving flutamide and 8 of 20 patients who received DES. Whereas

TABLE 3.—*Cost of Hormonal Treatment of Stage D Prostate Cancer*

Therapy	Cost Item	Cost/Item or Cost/Month, $*	Cost for 2 Years of Therapy, $
Bilateral orchiectomy	Surgeon fee	765	
	Hospital or other	1,193	
	Total	2,695	2,695
Diethylstilbestrol, 3 mg orally daily	1-mg tab	8	192†
Flutamide, 250 mg orally 3×/day	125 mg tab	299	7,176
Leuprolide acetate (Lupron Depot)	7.5 mg/ml	415	9,960
Goserelin (Zoladex), 3.6 mg subcutaneously every 28 days	3.6 mg pellet	322	7,728

*Reflects the average of 2 hospital or pharmacy estimates from the Albuquerque, New Mexico, area, based on June 1991 fees.

†Cost does not include excess cardiovascular morbidity for about 10% of patients, which has been estimated to add $1,600 to $2,000 per year to cost estimate for average patient (C. A. Olsson, "Cost of Diethylstilbestrol Underestimated," *AUA* [American Urological Association] *Today*, 1993 Feb; 6:3).

no substantial loss of libido or potency was noted with flutamide therapy, all of the patients receiving DES became impotent. Recent reports have suggested that flutamide may function as an agonist in patients treated with total androgen blockade. Prostate-specific antigen (PSA) levels declined, and clinical improvement was noted in several patients with apparent stage D3 prostate cancer when flutamide use was discontinued.[51] The main disadvantage of flutamide therapy is cost (see Table 3). Major side effects include gynecomastia (25% to 50%), severe diarrhea (10% to 15%), flushing (15% to 30%), and liver function abnormalities.[52]

Nilutamide. Nilutamide (Anandron) is an equipotent nonsteroidal antiandrogen with similar efficacy to flutamide as monotherapy; it is usually used in combination with medical or surgical castration.[53,54] Nilutamide has improved pharmacokinetics over flutamide, allowing doses of 300 mg per day. A recent prospective, randomized trial compared nilutamide with orchiectomy (n = 225) versus orchiectomy and placebo (n = 232). Significantly longer progression-free survival occurred for the nilutamide-treated group (20.8 months versus 14.9 months, ($P \leq .005$). Overall survival was not significantly different ($P \leq .07$).[55] The side effects of nilutamide are similar to those of flutamide, but also include brief impairment of adaptation to dark (an incidence as high as 90%) and interstitial pneumonitis (1% to 3%).[56]

Casodex. Casodex, a new nonsteroidal pure antiandrogen, is currently undergoing Phase II and III trials. The drug competes with dihydrotestosterone for binding to the androgen receptor. The response of patients with stage D prostate cancer to antiandrogens has been similar to that seen with conventional hormonal therapy.[48-50] No convincing benefit has been shown for patients with hormone-refractory disease.[57]

5α-Reductase Inhibitors

Finasteride. This drug, a 5α-reductase inhibitor currently undergoing trials in Europe, acts to inhibit the conversion of testosterone to dihydrotestosterone in target cells. Side effects with the use of this drug have been minimal, and it only rarely interferes with sexual function. Tissue testosterone levels are elevated dramatically, and thus far early clinical experience with finasteride for the treatment of prostate cancer has been disappointing. In a multicenter, randomized, placebo-controlled study of untreated patients with stage D prostate cancer, only PSA levels showed a small decrease, with no change in prostatic acid phosphatase levels, serum testosterone levels, prostate size, or bone scan appearance.[58]

Steroidal (Mixed) Antiandrogens

Cyproterone acetate. Cyproterone acetate is a synthetic steroid with progestational activity. Although not approved for use in the United States, it has been used in Europe. Cyproterone acetate competes with testosterone and dihydrotestosterone for androgen receptors in the prostate, secondarily produces suppression of luteinizing hormone release, and inhibits dihydrotestosterone uptake into the nucleus.[59,60] Cyproterone acetate has also been reported to have cortisol-like action and to suppress corticotropin-adrenal function.[61] A large multicenter, randomized trial compared the intramuscular administration of cyproterone acetate, 300 mg per week, with that of estradiol, 100 mg per week.[62] Of 91 patients receiving cyproterone acetate, 83 (91%) had improved performance status versus 95% in the estrogen-treated cohorts. Side effects occurred in only 37% of patients treated with cyproterone acetate versus 94% of those treated with estrogen. A European randomized Phase III trial (European Organization for Research on Treatment of Cancer) of 210 patients compared the use of cyproterone acetate, 250 mg per day orally; medroxyprogesterone acetate, 500 mg intramuscularly three times per week for eight weeks and then 220 mg per day orally; and DES, 3 mg per day orally.[63] The five-year survival was 38% for DES, 32% for cyproterone acetate, and 14% for medroxyprogesterone acetate. Cardiovascular toxicity was 35% for DES, 19% for medroxyprogesterone acetate, and 10% for cyproterone acetate.[63]

Cyproterone acetate has also been used to block the flare phenomenon of LH-RH agonists.[64] Flare was successfully blocked in 23 patients treated with buserelin and cyproterone acetate, 150 mg per day orally.[65] But a randomized study of 71 patients with metastatic cancer that compared the use of an LH-RH agonist with an LH-RH

agonist plus cyproterone acetate showed no significant difference in progression rates (38% versus 41%, respectively) once the flare period had passed.[66] For stage D3 disease, 15 patients were treated with cyproterone acetate, 200 or 250 mg per day orally.[67] Pain abated in four of ten and voiding symptoms in one of four. Similar results with pain relief were noted in 12 of 19 patients and increased energy in 5 of 13.[59]

An important aspect of cyproterone acetate therapy is its reversibility, with the return of serum testosterone levels to normal after therapy is stopped.[68] Cyproterone acetate has also been reported to lose effectiveness with long-term use.[69] Cardiovascular side effects may occur in 10% to 15% of patients[63,68,70] and gynecomastia in 13%.[62] Several studies have shown mild serum prolactin elevations to the upper limits of normal with the use of cyproterone acetate.[68,71] In short, this drug provides excellent androgen deprivation, even in monotherapy, with minimal cardiovascular toxicity.

Megestrol acetate. A regimen of megestrol acetate (Megace), 80 to 100 mg per day, will reduce testosterone levels to just above castrate levels in one month with a concomitant decrease in levels of luteinizing hormone and follicle-stimulating hormone (FSH). With administration for as long as four to six months, however, megestrol loses some of its activity, and serum levels of testosterone, luteinizing hormone, and FSH rise but not back to normal levels.[72] Adrenal androgens, androstenedione, and dehydroepiandrosterone sulfate are also suppressed.[73] The antiandrogenic qualities of megestrol acetate are limited.[73]

Megestrol acetate, 120 mg per day intramuscularly, has been combined with low-dose DES, 0.1 mg per day orally. This provides a sustained decrease of testosterone to castrate levels and a blockade of adrenal androgens with fewer DES-related side effects. When 23 patients with stage D2 prostate cancer using this regimen were compared with 23 patients treated with castration or DES, 1.0 to 3.0 mg per day, the median time to progression was found to be similar but slightly favored the use of DES plus megestrol—21 versus 16 months.[73] A regimen of DES, 3 mg per day, was compared with that of megestrol acetate plus DES, 0.1 mg per day. There were no differences in time to progression or survival, but less toxicity was seen with the use of megestrol and low-dose estrogen.[74] Even at very low doses, however, when combined with megestrol, estrogen can cause edema and gynecomastia.[75] Megestrol is not appropriate for monotherapy, but in combination with low-dose estrogens may be another regimen for achieving total androgen blockade.

Adrenal Suppression

Bilateral adrenalectomy was performed in 1945 by Huggins and Scott in four patients in whom initial hormonal therapy for prostate cancer had failed.[76] Due to a lack of glucocorticoid replacement, survival was less than 11 days in three patients. One patient survived 116 days. Minimal success was also reported in 1953.[77] With cortisol replacement, bilateral adrenalectomy became possible. In a review in 1973, objective responses were rare.[78] Thus, further efforts have been aimed at medical adrenalectomy.

Administering aminoglutethimide inhibits both testicular and adrenal steroidogenesis by blocking cytochrome P-450 hydroxylation of C21, C11, and C18 steroids and the conversion of cholesterol to pregnenolone.[79] Glucocorticoid replacement is necessary with treatment. Aminoglutethimide has been used primarily as a second-line treatment in patients who have progression of disease after standard endocrine therapy (stage D3).[31]

Ketoconazole administration also inhibits the synthesis of both testicular and adrenal androgens by blocking the cytochrome P-450 of C14 to 20 lyase, 17 to 20 desmolase, and 12-hydroxylase.[80] Ketoconazole has also been used as a second-line drug in patients for whom initial hormone therapy has failed. In addition, it is used when a rapid reduction in serum testosterone levels is necessary, such as for patients presenting with disseminated intravascular coagulation or impending spinal cord compression in whom orchiectomy is not possible. Ketoconazole therapy at 400 mg administered orally every eight hours will reduce serum testosterone levels to castrate levels in 24 hours.[81] The effect of ketoconazole is reversible after therapy is stopped. Complications of ketoconazole therapy may include severe hepatitis (1 per 16,000, usually reversible), a loss of libido, weakness or lethargy, and glucocorticoid deficiency.[82-84] Ketoconazole has also been used empirically, as initial therapy or in combination with LH-RH analogues.[84] Ketoconazole is not effective for hormone-refractory disease, however.[82]

Direct Cytotoxic Effect

In the treatment of prostatic cancer, low-dose estrogens exert their effect through the pituitary-gonadal axis. High-dose estrogens have a direct cytotoxic effect. Diethylstilbestrol has been shown to have inhibitory effects on DNA and RNA synthesis in both benign and malignant prostatic tissue.[85] It inhibits RNA polymerase activity in prostate tissue.[86] Stilbestrol diphosphate, a biologically inactive estrogen, when administered intravenously is converted by acid phosphatases to DES. Because stilbestrol diphosphate is water soluble, it can be administered in high doses.[25] Protein synthesis is inhibited in prostatic carcinoma cells isolated from culture by DES concentrations of 1 to 5 μg per ml.[26] Concentrations of DES of 25 μg per 10 grams of prostate tissue were found in prostatectomy specimens 30 minutes after stilbestrol diphosphate was administered intravenously.[87] Clinical evidence has also shown intravenous stilbestrol diphosphate to be effective in hormone-refractory prostate cancer. A beneficial effect of high-dose stilbestrol in 34 patients refractory to a standard oral dose of DES was first reported in 1955.[88] With the intravenous administration of 250 to 1,250 mg of stilbestrol diphosphate over 20 minutes daily, 26 patients (76%) had subjective responses, but only 3 (9%) of these had objective responses.[88] In another study, 29 patients were given high doses of stilbestrol diphosphate; 22 (76%) had lessened bone pain, and 13 (45%) had a significant fall in PSA levels (44% to 93.4% of pretreatment levels).[25] Of

19 other patients with hormone-refractory disease who were treated, 11 (58%) showed improvement.[89] Stilbestrol diphosphate was given for seven to ten days as a slow intravenous push of 1,100 mg or by 20-minute infusion of the same dose in 200 ml of a saline solution.[90] Rapid administration can cause perineal pain, nausea and vomiting, and bone pain in patients with widespread bony metastases. Pulmonary embolism, myocardial infarction, cerebrovascular accidents, and deep venous thrombosis are rare if the course is limited to seven days. The duration of response for a seven-day course is 3.8 ± 1.6 months if the PSA level declines. With no decline, a subjective response lasts only two months.[25] Patients with hormone-refractory disease with severe bone pain, uremia, or spinal collapse should be considered for intravenous stilbestrol diphosphate treatment.

Total Androgen Blockade

The concept of total androgen blockade in endocrine therapy for prostate cancer was pioneered ten years ago. Patients treated with an LH-RH analogue (leuprolide acetate) who also received an antiandrogen (flutamide) showed improved survival over historical controls.[91] There is clinical evidence that adrenal androgens may play a minor role in prostate cancer.[92-94] Adrenal androgens, androstenedione and dehydroepiandrosterone, account for 5% to 10% of circulating androgens in men and may be converted to dihydrotestosterone.[95,96] Furthermore, conventional endocrine therapy decreases serum testosterone levels about 95%, whereas prostate dihydrotestosterone levels fall only 60%.[14] The use of antiandrogens was theorized to block this residual androgen production and lead to total androgen blockade. If hormonal therapy fails, adding an antiandrogen may benefit some patients. Initial data from nonrandomized studies in hormone-refractory patients showed a 40% response rate.[10,91,96]

The introduction of LH-RH analogues and antiandrogens promoted an interest in total androgen blockade as primary therapy. In 1985 the National Cancer Institute Intergroup Study compared the use of leuprolide plus flutamide with that of leuprolide plus placebo in a double-blind randomized trial involving 603 previously untreated patients with stage D2 prostate cancer.[13] The median time to progression was 16.5 months for the combined therapy group and 13.9 months for the monotherapy group ($P \leq .039$). Median survival was 35.6 and 28.3 months, respectively ($P \leq .04$). Mild diarrhea was more common in the combined therapy group. The incidence of other side effects of nausea and gynecomastia was similar for both groups. Patients with minimal disease and good performance status benefited more and had not yet reached median survival at the trial's conclusion. The combination therapy produced less flare. The five-year follow-up on this study showed that the patients with minimal disease had reached the median time to progression and survival.[97] In the patients receiving combination therapy, the median time to progression was 58.3 months and survival 61 months versus 19.1 months and 41.5 months in the matched group who received leuprolide plus placebo. Patients with minimal disease had a 20-month survival advantage with combination therapy.

These results have been disputed, however. In a series of experiments using the Dunning rat tumor model, rats receiving orchiectomy plus flutamide had tumor growth and survival rates that were no better than those of rats receiving orchiectomy alone.[98] A randomized trial of 327 European patients with locally advanced or metastatic prostate cancer compared the use of orchiectomy versus that of goserelin plus flutamide, 250 mg three times a day.[99] The median time for follow-up was 1.5 years, and the median duration of survival was approximately 2.5 years in both groups. The time to the first objective evidence of progression or subjectively noted progression was substantially better for those given goserelin plus flutamide, but no difference in overall survival was seen. In another study, the use of the LH-RH analogue buserelin with and without cyproterone acetate was compared. No superiority of total blockade over testicular suppression alone was seen.[66]

Finally, a recent study from the International Prostate Cancer Study Group compared the use of goserelin with flutamide with its use alone in a randomized prospective trial of 571 previously untreated patients with locally advanced or metastatic prostate cancer.[100] After a median follow-up of two years, there was no difference in subjective or objective response rates, interval to progression (combination therapy, 760 days versus monotherapy, 985 days), or survival (median survival of 34.9 months in each group). In addition, increased gastrointestinal and liver toxicity in the combination-therapy group resulted in 44 patients being withdrawn from the trial.

Results of these studies suggest that patients with good performance status and minimal disease derive the greatest benefit from total androgen blockade, and this subgroup of patients should be targeted for therapy. Cost issues (see Table 3) are a consideration. Studies that show benefit of orchiectomy combined with the use of an antiandrogen, eliminating the more costly LH-RH analogue from the regimen, are encouraging from this perspective.

Early Versus Late Therapy

The early initiation of hormonal therapy—before symptoms appear—after the diagnosis of prostate cancer versus delaying therapy until symptomatic disease supervenes is controversial. In the 1950s instituting hormonal therapy immediately was thought fundamental to improved survival of patients with prostate cancer. This approach of promptly starting hormonal therapy was based primarily on three studies that showed improved survival of patients treated with orchiectomy or DES versus controls from the 1930s.[9,101,102] In the mid-1960s, however, the Veterans Administration Cooperative Urological Research Group's first trial compared four treatments—placebo; bilateral orchiectomy; DES, 5 mg per day; and DES plus orchiectomy—in 1,764 patients with stages C and D disease.[103] Most patients in the placebo group whose disease progressed were begun on hormonal therapy (70% in stage C and 100% of stage D). Therefore, this trial allowed for a comparison of early-versus-delayed hormonal therapy. No

survival benefit was seen. The second trial, VACURG II, studied different doses of DES—placebo, 0.2 mg, 1 mg, and 5 mg.[32,33] Initial results showed similar survival among the treatment groups, implying that there was no difference between delayed (placebo) and early hormonal therapy. In a retrospective study, 100 untreated patients with stage C and D disease from the Johns Hopkins (Baltimore, Maryland) Tumor Registry from the prehormone era (1937 to 1940) were compared with 100 similar patients treated with hormonal therapy (1942 to 1943). The date of diagnosis rather than the timing of hormonal therapy was found to have the greatest effect on survival.[104]

On the other hand, in the early 1980s studies of animals showed a benefit with early hormonal therapy. Late-versus-early hormonal treatment with androgen ablation, chemotherapy, or both was evaluated in Dunning R-3327 rats with prostatic adenocarcinoma. Animals who received early therapy had improved survival.[105,106] In a series of nonrandomized trials of patients with stage D disease treated with pelvic lymphadenectomy, radical prostatectomy, and immediate adjuvant therapy, disease-free survival was improved, but not overall survival. Five- and ten-year disease-free progression rates were 84% and 80%, respectively, for the early orchiectomy group versus 48% and 38%, respectively, with delayed therapy.[107] Other reports showed improvement in time to progression but no notable survival benefit.[108,109] A retrospective review was done of 68 patients with stage D1 disease who had 60 months of follow-up. Of these, 30 underwent immediate hormonal therapy and 38 had delayed treatment until the onset of bone metastases. The median interval to the appearance of bone metastases was 43 months in the delayed-treatment group and 100 months in the early-treatment group. The median interval to death was 90 versus 150 months, respectively, which shows a trend toward improved survival but was not statistically significant.[110] In 1988 the VACURG II data were reanalyzed, revealing a survival benefit with early hormonal therapy but only in patients younger than 74 years, who had higher grade tumors (Gleason's sum 7).[111] A mathematical model had been used to show a benefit of early therapy for younger patients with higher grade tumors.[112]

A poor prognosis has been shown for patients with aneuploid tumors despite early hormonal therapy.[107,113] The clinical course of 62 patients with stage D1 cancer was retrospectively analyzed and the DNA ploidy of paraffin-embedded tissue retrospectively determined.[114] Patients with diploid tumors receiving early endocrine therapy had improved disease-free survival. Although the intergroup study was not specifically designed to look at early-versus-delayed therapy, patients with minimal and presumably earlier disease who had good performance status (according to the ECOG standards) had longer survival free of progression and an increased median length of survival than did patients with severe disease and poor performance status.[13]

A number of factors correlate with metastatic potential or progression to the androgen-insensitive state. These include a high histologic grade,[115] aneuploidy,[113,116,117] more than six areas of uptake on a bone scan,[118] a volume greater than 1 ml,[119] a rising Gleason score,[16] a serum testosterone level before initiating therapy of less than 300 mg per dl,[16,118] and amplified *ras* and *myc* oncogene expression.[120]

Summary

The mainstay of the treatment of advanced prostate cancer is hormonal therapy. Orchiectomy, if acceptable to the patient, is the treatment of choice in terms of cost and compliance for patients with advanced disease and poor performance status. Antiandrogens are the first-line drug for patients wishing to maintain potency. The early initiation of hormone therapy shows some promise. Combination therapy may offer substantial benefit to patients with minimal disease and good performance status but possibly at great expense. Once a tumor becomes refractory to hormone therapy, current therapeutics are of minimal benefit.

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